GP1616

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REISSUE PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	SCHNEIDER, Michel et al.	) Group Art) No. 1616
Reissue of Patent No.:	5,413,774	)
Issued:	May 9, 1995	)
Appl. No.:	09/115,963	)
FOR:	LONG LASTING AQUEOUS DISPERSIONS OR SUSPENSION OF PRESSURE-RESISTANT GAS-FILLED MICROVESICLES AND METHODS FOR THE PREPARATION THEREOF	)
Examiner:	G. Hollinden	)
Attorney Docket No.:	80386-0000002	)

CERTIFICATE OF MAILING

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

April 16, 1999
(DATE)

Robert J. Lindell

TRANSMITTAL OF PROTEST UNDER 37 CFR 1.291(a)

Assistant Commissioner for Patents
Washington, DC 20231

Dear Sir:

Enclosed for filing in the above-identified Patent Application are the following documents:

(1) a Protest Under 37 CFR 1.291(a);

(2) Exhibits A-K; and

(3) a statement authorizing the Commissioner to charge any additional fees which may be required to Account No. 03-3975 under Order No. 80386-0000002; and

(4) a return pre-paid postcard.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

T. Tuck
#7
5/19/99

In re REISSUE APPLICATION f Michel Schneider et al.

Reissue of U.S. 5,413,774 Art Unit: 1616

Re. S.N. **09/115,963**

Patent granted May 9, 1995 Examiner: G. Hollinden

For: LONG LASTING AQUEOUS DISPERSIONS OR SUSPENSIONS OF PRESSURE-RESISTANT GAS-FILLED MICROVESICLES AND METHODS FOR THE PREPARATION THEREOF

Asst. Commissioner of Patents
Washington DC 20231

PROTEST UNDER 37 CFR 1.291(a)

This is a protest against the patentability of certain claims pending in the above-referenced reissue application.

Schneider et al. (Schneider) seeks reissue of United States Patent No. 5,413,774 (the '774 patent). The '774 patent originally contained claims 1-14. The pending claims appear to be 1-7 (8-12 have been cancelled) and 13-48. Original claims 1, 2 and 13 are amended.

This protest consists of this document and exhibits A-K submitted concurrently. **A complete copy of this protest and its exhibits have been served by first class mail on representatives of the patentee/reissue applicant, Nixon & Vanderhye, Attn: James T. Hosmer, 100 North Glebe Road, 8th Fl or, Arlington VA 22201-4714.**

CLAIMS AT ISSUE

This protest is directed to showing that claims 1, 4-7, 13-17, 23-29 and 31-40, 42-46 and 48 of the '774 patent are unpatentable over the prior art.

Protestor does not address the patentability of claims 2, 3, 9-12, 18-22 and 30 in this protest, although the issues raised in this protest are relevant to those claims to the extent that they are directed to the same subject matter, i.e., ultrasound contrast agents.

For reasons discussed below, protestor believes that claims 41 and 47 ARE PATENTABLE. (However, protestor SONUS Pharmaceuticals, Inc. is the assignee of an application currently in interference with the '774 patent/this reissue application, in which interference SONUS argues it (and not the assignee of this reissue application) is entitled to claims directed to the subject matter of claims 41 and 47).

INFORMATION ON WHICH THE PROTEST IS BASED

Protestor includes for the Examiner's attention the following Exhibits discussed below:

Exhibit A	Tickner et al., U.S. Patent 4,276,885
Exhibit B	Ryan et al., U.S. Patent 4,900,540
Exhibit C	Rossling et al., U.S. Patent 5,501,863
Exhibit D	Stein et al., PCT published application WO 89/06978
Exhibit E	Albayrak et al., PCT published application WO 90/01952

Exhibit F	Berwing et al., U.S. Patent 4,832,941
Exhibit G	Hilmann et al., U.S. Patent 4,466,442
Exhibit H	Tickner, U.S. Patent 4,265,251
Exhibit I	DuPont Technical Bulletin, "FREON", copyright 1964
Exhibit J	Reexamination No. 90/004,657, Response filed September 28, 1998
Exhibit K	Interference No. 103,881, Declaration of Johnny Lai

BACKGROUND

At the outset, it is relevant to this protest that the '774 patent specification acknowledges that "microballoons" and "microbubbles" (collectively, "microvesicles") containing ultrasound contrast agents were already known when that specification was filed:

> [A] It is well known that microbodies or microglobules of air or gas (defined here as microvesicles) e.g. microbubbles or microballoons, suspended in a liquid are exceptionally efficient ultrasound reflectors for echography. [Col. 1/23-27]
>
> ***
>
> [B] The microvesicles in aqueous suspension containing gases according to the invention include most microbubbles and microballoons disclosed until now for use as contrast agents for echography. [Col. 4/30-33]

Thus, one focus of the '774 patent was the identification of certain gases for use in such known carriers:

> [C] The gaseous species which particularly suit the

> invention are, for instance, halogenated hydrocarbons like the freons and stable fluorinated chalcogenides like SF_6, SeF_6 and the like. [Col. 7/65-68]

Fundamentally, claims 1, 4-7, 13-17, 23-29 and 31-40, 42-46 and 48 are unpatentable over the prior art since these claims recite known methods of making ultrasound contrast agents which refer to carriers already disclosed for use in ultrasound contrast and which refer to gases previously used in ultrasound contrast agents.

WHAT THE PRIOR ART TEACHES

Tickner et al. 4,276,885 (Exhibit A) is effective as a reference May 4, 1979. It discloses ultrasonic image enhancement (col. 1/6-8), using microvesicles formed by a surface membrane encapsulating a gas of a selected composition (col. 2/42-44). In Tickner, the preferred membrane is gelatin (col. 3/54-55), and the gas is selected from nitrogen, noble gases and carbon dioxide (col. 4/16-20 and 28-29).

Ryan et al. 4,900,540 (Exhibit B) is effective as a reference June 20, 1983. It discloses the use of amphiphilic liposomes to encapsulate a gas and thus form an ultrasound contrast agent. See col. 1/7-26; col. 2/9-17; col. 2/33-45; col. 2/49-51. The patent states, at col. 2/38-45:

> The liposomes can be unilamellar or multilamellar and can be formed from any lipid material ... Representative suitable lipid materials that can be utilized to form liposomes include distearoyl phosphatidylcholine and/or ... dipalmitoyl phosphatidylcholine or similar lipid substances. The walls of the liposomes can also be formed from soybean phospholipid ...

The gases encapsulated within the liposomes include carbon dioxide, helium, argon, xenon, etc. See col. 2/54-58.

Rossling 5,501,863 (Exhibit C) is effective as a reference February 11, 1991. It discloses aqueous ultrasonic contrast media utilizing microvesicles formed of a biodegradable polymer encapsulating a gas. See col. 1/52 to col. 2/9. The encapsulated gases include SF_6 (col. 3/46) which is a preferred gas (col. 4/22-23), "halogenated hydrocarbons" (col. 4/6), such as, for example CBr_2F_2 (col. 4/11), and many, or most, of the other gases used in the prior art. Rossling also discusses prior art to itself, which includes free gas microbubbles stabilized with sugars, sugar alcohols and surfactants (col. 1/16-45, particularly at lines 39-41), as ultrasound contrast enhancing agents.

Stein et al., PCT WO 89/06978 (Exhibit D), published August 10, 1989 discloses an ultrasonic contrast agent consisting of microvesicles of a biodegradable polymer containing a gas. See the abstract and pp. 5-6. The polymers suggested include as "particularly suitable" polylactic acid (p. 5) and "copolymers of lactic acid and glycolic acid" (p. 5). Also included are poly(alkylcyanacrylates) and poly(epsilon-caprolactone) (p. 5). Among the preferred gases is dibromodifluoromethane (CBr_2F_2)(p. 6). A procedure for forming the gas-filled microvesicles is described at p. 8 and claim 17, wherein gas bubbles are produced in an aqueous solution or dispersion of monomer, to which is added a polymerization initiator and crosslinker to form the encapsulated gas bubble microvesicles.

Albayrak et al., WO 90/01952 (Exhibit E), published March 8, 1990, discloses ultrasonic contrast agents formed of cavitate-or clathrate-forming carriers in host/guest complexes (abstract and p. 3). The guest molecules include "halogenated hydrocarbons" and sulfur hexafluoride (SF_6)(p. 4). Other gases include lower hydrocarbons, nitrogen, and the rare or noble gases and carbon dioxide (p. 4). In use, the host/guest complexes are introduced into an aqueous vehicle, where the host portion dissolves, releasing the gas bubbles (p.4), as indicated by "passage through the pulmonary capillary bed" on p. 5.

Berwing et al. 4,832,941 (Exhibit F) is effective as a reference August 14, 1986. It discloses an ultrasonic contrast agent (col. 1/6,7) formed of free gas microbubbles in an aqueous vehicle which may be stabilized by the addition of "a sugar alcohol, such as sorbitol" (col. 3/9-12) and "a phospholipid, such as lecithin, which acts as a surface-active agent and stabilizes the microscopic gas bubbles" (col. 3/13-18). The gas bubbles are formed in the presence of the gas by "spraying the liquid backwards and forwards in the gas atmosphere 25 times via a three-way tap" (col. 3/51-64).

Hilmann et al. 4,466,442 (Exhibit G) is effective as a reference October 13, 1982. First, it is noted that the word "tenside" used in this reference is acknowledged in the '774 patent to mean surfactant. See, e.g., the '774 patent at col. 1/57-58, "a solution of a tenside (surfactant) in a carrier liquid". Hilmann teaches a suspension of microbubbles as a contrast agent for ultrasound (col. 1/9-27), in an aqueous carrier liquid, containing tensides and viscosity-raising compounds dissolved

therein or as a colloidal dispersion (col. 6/13-17). The tenside (i.e. surfactant) may be "lecithins, lecithin fractions and their modification products" (col. 5/25-26), and other well-known surfactants (col. 5/26-39), and mixtures thereof (col. 5/44-45). The viscosity-raising compounds include sorbitol and other mono- or polysaccharides (col. 5/51-59). Hilmann also states at col. 6/64-68:

> In carrying out the method of this invention, microbubbles are introduced into the selected carrier liquid, e.g., by mechanical agitation, to produce a suspension of microbubbles in the carrier liquid containing both a tenside [surfactant] and a viscosity-raising compound ...

and then at col. 9/45-49:

> The tenside insures that a large population of microbubbles with diameters less than 50 [microns] will be produced and the viscosity-raising agent ensures the stability and an acceptable lifetime of that population.

Tickner 4,265,251 (Exhibit H) is effective as a reference June 28, 1979. It discloses the use of free gas microbubbles in a cardiovascular system (col. 3/23-33), "to provide an enhanced ultrasonic image" (col. 7/9-12). The gas in the microbubble is selected from a plurality of physiologically acceptable gases listed at col. 6/62 to col. 7/2, including a mixture of the gases. Among the listed gases is "freon" (col. 6/66). "Freon" compounds are "organic compounds containing one to four carbon atoms and fluorine . . . [c]hlorine, bromine and hydrogen atoms also may be present." (see p. 1 of a DuPont Technical Bulletin attached hereto as Exhibit I).

ARGUMENT

BACKGROUND

The use of gas microbubbles as contrast enhancing agents for ultrasound imaging is very old, and is disclosed, for example, in the Tickner patent as of May 4, 1979. The prior art has long recognized two forms for such microbubbles. The first form is as free gas microbubbles, i.e., as bubbles of gas suspended in an aqueous vehicle with a gas/liquid interface defining the physical perimeter of the bubble, with or without a bubble stabilizer in the aqueous vehicle. For example, the Rossling patent (effective as of February 11, 1991) discloses that prior art to Rossling provided ultrasound contrast agents in the form of free gas microbubbles which could be stabilized with sugar, sugar alcohols and surfactants. Similarly, Berwing and Hilmann, disclose ultrasound contrast agents formed of free gas microbubbles in an aqueous vehicle, which may be stabilized by the addition to the vehicle of a sugar alcohol such as sorbitol, and a surfactant such as lecithin. Also note that Tickner discloses ultrasound enhancement agents formed of free gas microbubbles of freon gas. The second form is as encapsulated bubbles, i.e., gas bubbles whose physical perimeter is defined by a material envelope or encapsulant, such as a polymer, referred to by Schneider as "microballoons". For use as an ultrasound contrast agent, these microballoons are suspended in an aqueous vehicle. For example, the aforesaid Rossling patent discloses an ultrasound contrast agent utilizing a microballoon formed from a biodegradable polymer encapsulating a gas, such as SF_6, or a "halogenated hydrocarbon" such as CBr_2F_2. Both these gases are fluorinated gases. Similarly, the Stein PCT application

provides an ultrasound contrast agent utilizing microballoons formed from a biodegradable polymer encapsulating a gas. A preferred gas is the halogenated (or more specifically, fluorinated) gas, dibromodifluoromethane (CBr_2F_2).

In respect to Stein, there are several approaches to encapsulation disclosed. In one such approach (page 8, and at claim 17), gas bubbles are produced in a solution or dispersion of a monomer, and then the monomer is polymerized and/or cross-linked. That process will produce gas-filled microballoons very similar to the Schneider balloons.

In respect to the gas, in addition to Rossling and Stein, one should also note the Albayrak published application. There, solid "host" microparticles contain a "guest" gas, which can be a "halogenated hydrocarbon" or sulfur hexafluoride (SF_6). In use, the host/guest complex is placed in an aqueous vehicle, where the host particles dissolve, releasing the guest gas as bubbles.

In respect to the feature of forming the microbubbles or microballoons in the presence of the gas, that, too, is commonplace in the prior art. For microbubbles, see, for example, the Berwing patent. Berwing forms an ultrasound contrast agent of free gas microbubbles in an aqueous vehicle that may be stabilized. The gas microbubbles are formed in the presence of the gas by spraying the aqueous vehicle "backwards and forwards in the gas atmosphere" by means of a three-way stopcock. For microballoons, see, for example, the Stein published application. Stein forms an ultrasound contrast agent by dispersing the gas bubbles in a solution or dispersion of

monomer, to which is added a polymerization initiator and crosslinker to form the microballoons in the presence of the gas.

THUS, ALL THE CONCEPTS INVOLVED IN THE CLAIMS AT ISSUE HERE ARE OLD. And it appears that even Schneider acknowledges this in its specification.

Referring to the claims at issue, the key feature in every claim is the gas used to form the microbubbles or microballoons. The basic claims recite a large Markush group of fluorinated and halogenated gases and some of the dependent claims recite one or another, or a sub-Markush group of those gases. But several of those Markush gases are specifically taught in the prior art for use as ultrasound contrast agent microbubbles. Rossling teaches the use of SF_6 and "halogenated hydrocarbons", such as the fluorinated hydrocarbon CBr_2F_2; Stein also teaches the use of CBr_2F_2; and Albayrak, teaches the use of "halogenated hydrocarbons" and SF_6. The original Schneider Markush group includes CBr_2F_2, SF_6 and numerous halogenated hydrocarbons. "It is well settled that a generic claim [Schneider's Markush group] cannot be allowed to an applicant if the prior art discloses a species [CBr_2F_2 or SF_6] falling within the claimed genus." In re Slayter, 276 F2d 408, 125 USPQ 345, 347 (CCPA 1960). Also see In re Goodman, 11 F3d 1046, 29 USPQ2d 2010, 2016 (Fed. Cir. 1993); Titanium Metals Corp. vs. Banner, 778 F2d 775, 227 USPQ 773, 779 (Fed. Cir. 1985). In addition, Tickner discloses the use of freon gas for ultrasound enhancement and many of the Schneider claimed Markush group gases are freons. A genus disclosed in the prior art [freons] renders a species falling within that genus *prima facie* obvious and unpatentable, unless unexpected results with that species can be shown.

In further regard to the aforesaid reissue application Markush group of gases, we will comment on the deletion of two gases from the Markush group of halogenated gases used in the Schneider original patent claims. In the reissue application, CCl_2F_2 and CBr_2F_2 have been deleted from the claimed Markush group of gases. The reissue application gives no reason or explanation whatsoever for these deletions. We suspect this is simply an arbitrary deletion to appear to avoid prior art that recites these specific gases. However, that is of no avail. The original Markush grouping is an assertion or acknowledgment that all recited members are functionally equivalent for purposes of the subject matter claimed (a Markush group in a claim is an assertion by the patentee that there exists a "unity of invention" among the claimed elements). In re Hirnisch, 631 F2d 716, 206 USPQ 300 (CCPA 1980). See also Ex parte Burke, 21 USPQ 399, 401 (Comm'r Pats 1934) ("In every Markush formula all of the members must fall in the same natural physical or chemical class and should of course, have equivalence in function in the claimed process or composition." Emphasis added.) Thus, the fact that CBr_2F_2 (dibromodifluoromethane) is arbitrarily removed from the reissue claims Markush group in no way diminishes its previously asserted equivalence to the remaining members of the Markush group. Therefore, its presence in the prior art for the same purposes as claimed by Schneider renders the claimed Markush group unpatentable, whether or not the CBr_2F_2 is now recited in the Markush group. The compound CBr_2F_2 is still equivalent to the other members defined by the Markush group, rendering the residual Markush group unpatentable. In re Slayter, supra.

CLAIM BY CLAIM ANALYSIS

Addressing the aforesaid Schneider reissue application claims seriatim, claim 1 is to an ultrasound contrast agent of "microbubbles bounded by an evanescent gas/liquid interfacial closed surface", wherein the gas is selected from a Markush group of fluorinated gases, and the microbubbles are formed in the presence of the gas. All of the gases except for SF6 and SeF6 are freons, a "genus" that is acknowledged prior art. The recited gases still include SF_6, and originally included CBr_2F_2. The claim also recites that the microbubbles are resistant to collapse from bloodstream pressure; but, no feature is recited to support this function except the inherent property of the bubble, presumably the gas, as is explicitly stated in claim 13 and in the Schneider patent specification at col. 3/63 to col. 4/7.

Berwing discloses an ultrasound contrast agent formed of free gas microbubbles in an aqueous vehicle. The bubbles are formed in the presence of the gas, but the gas is not a fluorinated gas. However, Rossling discloses the use of the fluorinated gases SF_6 and CBr_2F_2, and "halogenated hydrocarbons" for this purpose, and discloses the formation of both free gas microbubbles and microballoons for this purpose. Stein discloses CBr_2F_2, and Albayrak discloses the use of free gas microbubbles of SF_6, for this purpose. Similarly, Tickner discloses the use of freon gas for this purpose. And many of the Schneider fluorinated Markush group gases are freons. Since the use of these gases is prior art, their inherent resistance to collapse is also prior art.

It would be obvious to use the Rossling, Stein, Tickner or Albayrak gases in making the Berwing contrast agent. In this regard, it should be noted, as indicated

above, that both free gas microbubbles and encapsulated microbubbles (i.e., microballoons) are both well-recognized modes of delivering ultrasound contrast agent gases, and the Schneider specification itself equates microbubbles and microballoons (see col. 1/23-45), and their equivalency is repeated in the original patent claims (see patent claim 1). Schneider reissue application claim 1 is therefore unpatentable.

Reissue application claims 4-7 depend from reissue claim 1, and add a lamellar surfactant (claim 4), which is a phospholipid (claim 5), in the form of liposomes (claim 6), and is a C_{16} or higher diacylphosphatidyl compound (claim 7). All this is expressly taught in the ultrasound contrast agent of Ryan. In Ryan it appears that the phospholipid is used as an encapsulant for the microbubbles, while it appears that Schneider claims 4-7 are directed to the addition of the lipid to the aqueous vehicle as a free gas microbubble surfactant stabilizer. However, Berwing uses a phospholipid, such as lecithin, and Hilmann also uses lecithins dissolved, or as a colloidal dispersion, in the aqueous carrier, as surfactants to stabilize the free gas microbubbles. It would be quite obvious to use the specific phospholipids of Ryan as the phospholipid surfactants in Berwing and Hilmann. Clearly, Schneider dependent claims 4-7 do not add any patentable feature to claim 1, and these claims are also unpatentable in view of the prior art.

Reissue application claims 13 and 14 are substantively identical to reissue application claim 1, and therefore are unpatentable for the same reasons as expressed hereinabove in respect to reissue claim 1. The primary difference between these claims is that the limitation of resistance to bubble collapse (discussed in respect to reissue

application claim 1) is expressly stated to be an inherent property of the gas in these claims 13 and 14 -- "said gas being such that [it is resistant to collapse under bloodstream pressure]". Therefore, these claims 13 and 14 are likewise unpatentable in view of the prior art.

Reissue application claim 15 is nearly identical to reissue application claim 1. Where claim 1 recites:

> ... forming the microvesicles in the presence of a physiologically acceptable gas ...

claim 15 recites instead:

> ... forming the microvesicles in the presence of a gas mixture comprising a physiologically acceptable gas ...

Otherwise, the two claims are verbatim identical. Thus, claim 15 merely requires broadly the use of two (or more) components in the gas, whereas claim 1 provides for the use of one or more components in the gas. Berwing specifically recites the use of one of a number of gases "or mixtures thereof" (see col. 3/53); and the same is also true of Stein, Q/DX-6, see page 6/11 and 35. (The Stein gas mixture therefore includes dibromodichloromethane and any other of the enumerated gases.) Likewise, Tickner, Q/DX-25, suggests using a mixture of gases. Clearly, there is no patentable distinction between claim 15 and claim 1, and claim 15 is unpatentable in view of the prior art, for the same reasons as expressed above with respect to claim 1.

Reissue application claim 16 differs from reissue application claim 1 merely in reciting "microballoons" (claim 16) in lieu of "microbubbles" (claim 1), and reissue application claim 17 differs from claim 16 merely in reciting a "gas mixture"

(claim 17) in lieu of "a ... gas" (claim 16). Since microballoons and microbubbles are well-known alternatives in this art of ultrasound contrast agents, as discussed previously, claim 16 is unpatentable for the same reasons as expressed above in respect to claim 1. Claim 17 (mixture of gases) is unpatentable for the same reasons as expressed above in respect to claim 15. Furthermore, since these claims are to microballoons, Stein is particularly relevant, in disclosing the use of a polymer encapsulating a mixture of dibromodifluoromethane and another disclosed gas. See Stein at page 6/11, 19 and 35. These claims 16 and 17 are clearly unpatentable in view of the prior art.

Reissue application claims 23-26 are identical to reissue application claims 4-7, except they depend from reissue application claim 15. They do not add any patentable feature over said claim 15 for the same reasons as stated above in respect to reissue application claims 4-7. Therefore, these reissue claims 23-26 are unpatentable in view of the prior art.

Reissue application claims 27 and 28 depend from reissue claims 16 and 17, respectively, and reissue application claim 29 depends from reissue claims "27 or 28". Claims 27, 28 and 29 add the limitations that the microballoon envelope is a polymer (claims 27 and 28), and the polymer is polylactic or polyglycolic acid (claim 29). These are precisely the polymers used to form the microballoon envelopes in Stein. Thus, these claims 27-29 add nothing patentable to their parent claims 16 and 17, and are unpatentable in view of the prior art.

Reissue application claim 31 is identical to original patent claim 11, except it depends from reissue application claims "16 or 17", and recites a particular way of filling a microvesicle with a desired gas. However, this is a standard method and Schneider has not in any way disclosed any unique feature about it. Accordingly, claim 31 (like patent claim 11) adds nothing patentable to its parent claims "16 or 17", and claim 31 is unpatentable in view of the prior art.

Reissue application claims 32, 33 and 34 pertain to making an ultrasound contrast agent in the form of "gas-filled microbubbles" (claim 32) or "gas-filled microballoons" (claims 33 and 34) in an aqueous vehicle, wherein the microbubbles (claim 32) or microballoons (claims 33 and 34) are formed "in the presence of a gas mixture comprising a physiologically acceptable gas" (claims 32 and 34) or the microballoons are formed in the presence of a physiologically acceptable gas" (claim 33). The gas is selected from a Markush group of halogenated hydrocarbons, and is resistant to collapse when exposed to bloodstream pressure.

These claims 32, 33 and 34 are substantively identical to reissue application claims 15, 16 and 17, respectively. There are some language variations between the two groups of claims, but they have no substantive significance. Therefore, reissue application claims 32, 33 and 34 are unpatentable in view of the prior art for the same reasons that respective reissue application claims 15, 16 and 17 are unpatentable, as discussed above.

Reissue application claims 35 and 36 depend from reissue claims 32, 33 and 34. Claims 35 and 36 further define the resistance to bubble collapse included in

claims 32, 33 and 34. However, this feature is expressly defined as simply a property of the gas being used. See claims 35 and 36 which recite "the ... gas is such that [its resistance to collapse under pressure increase is defined in a certain pressure range]," and almost identical language in claims 32, 33 and 34. Since this feature is recited simply as an inherent property of the gas, and since at least one of the gases listed in the claimed Markush group is used in the prior art (as discussed above), these claims are clearly unpatentable.

Reissue application claims 37-48 are all dependent claims directed to specific gases from the Markush group genus of gases set forth in their parent reissue application claims 1, 15, 16 or 17. The original Markush group genus of these gases included SF_6, CBr_2F_2 and many gases known as freons which are shown in the prior art for the same purpose of ultrasound contrast enhancement, rendering the Markush group genus unpatentable. The reissue application claims remove CBr_2F_2 from the Markush group, but retain SF_6. The removal of CBr_2F_2 was probably simply an effort to appear to avoid the prior art. But that is of no avail, because the equivalence of all the original gases is acknowledged in the original Markush group genus. Ex parte Burke, supra. If one member or species of a genus is shown in the prior art, the entire genus is rendered unpatentable. In re Slayter, supra. However, if one can show unexpected substantially improved results or properties with respect to certain species of the genus, those species could be patentable. In re Hoch, 428 F.2d 1341, 166 USPQ 406, 409 (CCPA 1970); In re Soni, 54 F.3d 746, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995).

In other proceedings in the Patent Office evidence has been supplied that such unexpected substantially improved properties exist for C_4F_{10} gas for ultrasound contrast enhancement. This is shown in attached Exhibit J, which is a complete copy of a response filed in Reexamination No. 90/004,657 on Sept. 28, 1998, including exhibits thereto (which exhibits are numerically tabbed for convenience). Exhibit J includes the declaration of Dean Kessler. The data in the Kessler declaration are collected from experiments performed by art recognized methods and rely on *in vivo* studies in which a statistical analysis of the data is performed. The data reported in Mr. Kessler's declaration clearly establish two facts important to this protest: (1) that perfluorobutane C_4F_{10} has surprisingly superior ultrasound contrast characteristics (supporting the patentability of claims 41 and 47 in this reissue application), and (2) that other gases claimed in the reissue application, and that fall within the Markush group or generic language used in the reissue claims, DO NOT provide such unexpectedly superior results, such as C_4F_8 in claims 40 and 46 and CF_4, C_2F_6, and C_4F_8 in claim 1 and 2. The parent claims for these species claims, reissue application claims 1, 15, 16 and 17 with their Markush group of gases, are shown above to be unpatentable in view of the prior art. Since the gases identified in claims 37-48 are selected species or a "subgroup" taken from that Markush group, they, too, are unpatentable, unless a showing of unobviousness is made for a particular species, as was shown in the reexamination referred to above for C_4F_{10}.

Data which the Examiner may also find relevant to a determination of the patentability of claims in this reissue application are found in the Declaration of Johnny

Lai In Support of the Party Quay, which is attached hereto as Exhibit K. This declaration of Johnny Lai has been served on the parties in pending Patent Office Interference No. 103,881 and describes the *in vitro* testing of various microbubbles of gases, including many of the gases recited in the claims in this reissue application. While consideration of the details of the declaration is left to the Examiner, protester points out Table 2 at pages 13 and 14 of the Lai Declaration which summarizes the results of the tests on bubbles in saline, and Table 4 which tested a range of gases stabilized by phospholipids. Ultimately, it can be seen from the Lai data that microbubbles of virtually all of the individual compounds mentioned in the reissue claims were relatively short-lived. Only perfluoropropane, perfluorobutane, perfluorocyclopentane, perfluoropentane and perfluorohexane produced unusually high persistence. Of these chemicals, of course, only perfluorobutane is mentioned in the reissue claims.

Mr. Lai also notes that he did not test selenium hexafluoride since it is rated as a "Class A" poison by the US DOT, and that he could not obtain perfluorocyclobutane, chlorotrifluoromethane and bromochlorodifluoromethane. We do not understand why a poisonous gas would be claimed. In paragraph 23, Mr. Lai predicted that octafluorocyclobutane would be expected to have a persistence "a little less" than the value obtained for perfluorobutane. For perspective, the Examiner will note that Mr. Lai's work was done before the work reported in the declaration of Mr. Kessler. Mr. Kessler reported a persistence value substantially lower for octafluorocyclobutane than for perfluorobutane.

In light of the Lai and Kessler data, unless and until the reissue applicant provides a showing of unexpectedly superior performance for any of the remaining species, Schneider reissue claims 37-40, 42-46 and 48 are all unpatentable in view of the prior art, for the reasons explained above in respect to their parent claims 1, 15, 16 and 17 and their original Markush group.[1] Further, in light of the fact that different results were obtained by Lai (*in vitro*) and Kessler (*in vivo*) for perfluorocyclobutane, it is reasonable to require that any showing of unexpected results proposed by the reissue applicant must be (as with the Kessler data) obtained via art recognized methods, with *in vivo* imaging and proper statistical analyses.

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[1] An additional note in respect to the reissue claims 37 and 43 -- these are directed to a subgenus group of gases, CF_4, C_2F_6, C_4F_8 and C_4F_{10}. Since this subgenus includes unpatentable species from the original Markush group genus, the subgenus as a whole is unpatentable, despite the aforementioned showing in the reexamination proceeding that perfluorobutane is patentable. In re Slayter, supra.

Thus, all of the Schneider reissue application claims discussed are unpatentable in view of the prior art, except for claims 41 and 47.

Respectfully Submitted,

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